



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/22050 <b>(22) International Filing Date:</b> 5 December 1997 (05.12.97)  <b>(30) Priority Data:</b> 60/032,636 9 December 1996 (09.12.96) US 9700220.8 8 January 1997 (08.01.97) GB  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> FUH, Vivian, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KAUFMAN, Keith, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WALDSTREICHER, Joanne [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING BONE LOSS  <b>(57) Abstract</b> <p>The present invention provides for a method of inhibiting bone loss in a subject in need of such treatment comprising administration of a therapeutically effective amount of a compound of structural formula (I) to the subject. The present invention further provides for a method for treating and preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, comprising administration of therapeutically effective amount of a compound of structural formula (I) to the subject. Further, the present invention provides for compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for inhibiting bone loss and treating or preventing osteoporosis and osteopenia.</p> <div data-bbox="974 1113 1429 1386"></div>		

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TITLE OF THE INVENTION  
METHODS AND COMPOSITIONS FOR PREVENTING AND  
TREATING BONE LOSS

5 FIELD OF THE INVENTION

The present invention provides for a novel method of preventing and/or treating bone loss. Further, the present invention is directed to methods of treating and/or preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be  
10 beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The present invention also provides for a method of manufacture of a medicament useful for inhibiting bone loss, and for preventing and/or  
15 treating osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The present invention also provides for compositions  
20 useful in the methods of inhibiting bone loss and treating and/or preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both  
25 vertebral and nonvertebral.

BACKGROUND OF THE INVENTION

The mechanism of bone loss is not well understood, but in practical effect, the disorder arises from an imbalance in the formation  
30 of new healthy bone and the resorption of old bone, with the result being a net loss of bone tissue. This bone loss includes a decrease in both mineral content and protein matrix components of the bone, and leads to an increased fracture rate of, predominantly, femoral bones and bones in the forearm and vertebrae. These fractures, in turn, lead to

an increase in general morbidity, a marked loss of stature and mobility, and, in many cases, an increase in mortality resulting from complications.

5 Bone loss occurs in a wide range of subjects including aging men and women, post-menopausal women, patients who have undergone hysterectomy, patients who are undergoing or have undergone long-term administration of corticosteroids, patients suffering from Cushing's syndrome, and patients having gonadal dysgenesis.

10           Unchecked, bone loss can lead to osteoporosis and/or osteopenia. Osteopenia is reduced bone mass due to a decrease in the rate of osteoid synthesis to a level insufficient to compensate normal bone lysis. Osteoporosis is a major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of  
15 bone spaces) without a reduction in bone volume, producing porosity and fragility.

          One of the most common types of osteoporosis is found in post-menopausal women affecting an estimated 20 to 25 million women in the United States alone. A significant feature of post-menopausal  
20 osteoporosis is the large and rapid loss of bone mass due to the cessation of estrogen production by the ovaries. Indeed, estrogens have been shown to limit the progression of osteoporotic bone loss, and estrogen replacement is a recognized treatment for postmenopausal osteoporosis in the United States and many other countries. Although the  
25 administration of estrogens have beneficial effects on bone when given even at very low levels, long-term estrogen therapy has been implicated in a variety of disorders such as an increase in the risk of uterine and breast cancer, vaginal bleeding, and endometrial hyperplasia, causing many women to avoid this treatment. Recently  
30 suggested therapeutic regimens which seek to lessen the cancer risk, such as administering combinations of progestogen and estrogen, may be linked to negative cardiovascular effects. Concerns over the significant undesirable effects associated with estrogen therapy, and the limited ability of estrogens to reverse existing bone loss, support the need  
35 to develop alternative therapy for bone loss that generates the desirable

effects on bone but does not cause undesirable effects.

Attempts to fill this need by the use of compounds commonly known as antiestrogens, which interact with the estrogen receptor, have had limited success, perhaps due to the fact that these  
5 compounds generally display a mixed agonist/antagonist effect. That is, although these compounds can antagonize estrogen interaction with the receptor, the compounds themselves may cause estrogenic responses in those tissues having estrogen receptors. Therefore, some antiestrogens, when administered alone, are subject to the same adverse effects  
10 associated with estrogen therapy.

Osteoporosis and osteopenia are present in both aging men and women, due to age-related bone loss.

Other treatments used for osteoporosis include vitamin and mineral supplementation with calcium and vitamin D. This has limited  
15 effectiveness in treating advanced disease and regular disease. The effectiveness of this treatment is limited in treating and preventing bone loss.

Treatment with bisphosphonates such as alendronate, currently marketed by Merck & Co., Inc. as FOSAMAX®, has also been  
20 successful in inhibiting bone loss and increasing bone density. Bisphosphonates have low bioavailability and their administration must avoid food interactions. Treatment with shots or intranasal Calcitonin and low dose PTH (parathyroid hormone) shots have also been employed in an effort to inhibit bone loss and treat or prevent  
25 osteoporosis. Treatment with calcitonin is associated with a high rate of allergic reaction.

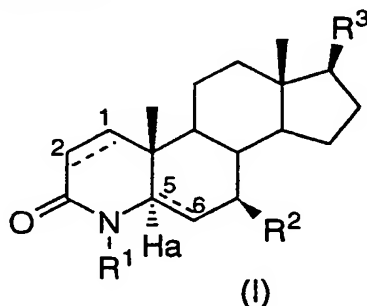
Treatments used for bone loss in men include vitamin and mineral supplementation with calcium and vitamin D. This has limited  
30 effectiveness in treating advanced disease and regular disease. The effectiveness of this treatment is limited in treating and preventing bone loss.

Also, bone loss in men is treated with androgens such as testosterone. Treatment with testosterone can lead to baldness, acne, lowering of HDL cholesterol (the "good" cholesterol) and raising of LDL

cholesterol (the "bad" cholesterol), and it may be associated with an increased risk of prostate cancer and benign prostatic hyperplasia.

U.S. 5,550,134, issued August 27, 1996, describes methods for inhibiting the loss of bone with benzoquinolin-3-ones known to be inhibitors of the enzyme 5 $\alpha$ -reductase type 1.

The present invention relates to methods of inhibiting bone loss without the associated adverse effects of hormone replacement therapy, and thus, serves as an effective acceptable treatment for osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. It has now been found that a 5 $\alpha$ -reductase type 1 inhibitors of structural formula I:



15

wherein:

the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;

R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and

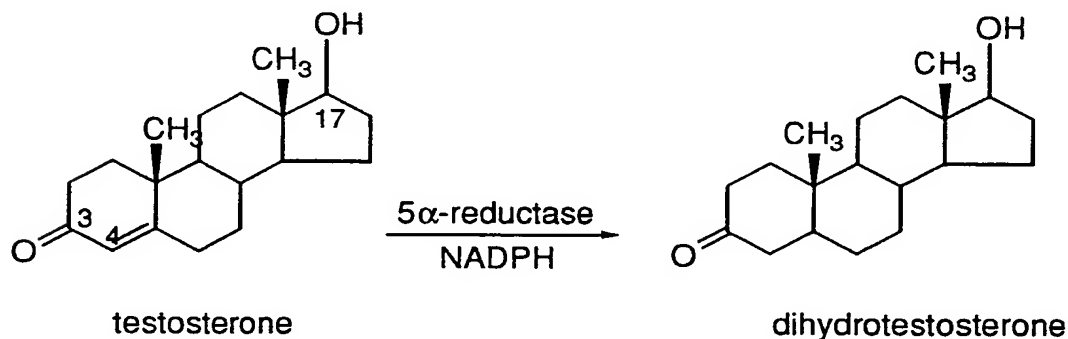
R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;

25

or a pharmaceutically acceptable salt, or stereoisomer thereof, are useful for the inhibition of bone loss and the treatment of the associated clinical conditions. In particular, the present invention relates to the use of compounds of structural formula I for the inhibition of bone loss

and the treatment and prevention of osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The inhibition of bone loss contemplated by the present methods includes both medical therapeutic and/or prophylactic treatment, as appropriate.

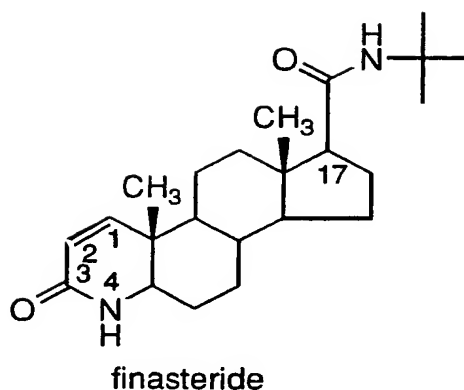
The enzyme 5 $\alpha$ -reductase catalyzes the reduction of testosterone (T) to the more potent androgen, 5 $\alpha$ -dihydrotestosterone (dihydrotestosterone" or DHT), as shown below:



**There are two isozymes of 5 $\alpha$ -reductase in humans.**

15 Andersson, et al., Proc. Natl. Acad. Sci. USA, 87:3640-44 (1990);  
Andersson, et al., Nature, 354, 159-61 (1991). The isozymes, usually  
called Type 1 and Type 2, exhibit differences in their biochemical  
properties, genetics, and pharmacology. Both isozymes are now the  
subject of considerable research and it has been found one isozyme (type  
20 1) predominates in the sebaceous glands of facial skin and skin tissue  
and that the other (type 2) predominates in the prostate.

Finasteride (17 $\beta$ -(N-tert-butylcarbamoyl)-3-oxo-4-aza-5 $\alpha$ -androst-1-en-3-one) as shown below, is a potent inhibitor of the human type 2 enzyme.

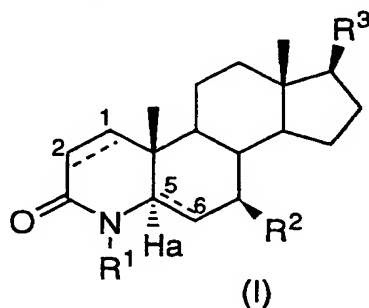


Under the tradename PROSCAR®, finasteride is known to be useful in the treatment of hyperandrogenic conditions, see e.g., U.S. 4,760,071.

- 5 Finasteride is currently prescribed for the treatment of benign prostatic hyperplasia (BPH), a condition affecting to some degree the majority of men over age 55. Finasteride's usefulness in the treatment of androgenic alopecia and prostatic cancer is described in the following documents: EP 0 285 382, published 5 October 1988, EP 0 285 383,  
10 published 5 October 1988 and Canadian patents 1,302,277 and 1,302,276.

### SUMMARY OF THE INVENTION

- The present invention provides for a method of inhibiting bone loss in a subject in need of such treatment comprising  
15 administration to the subject of a therapeutically effective amount of a compound of structural formula I:



wherein:

- the C1-C2 and C5-C6 bonds designated with a dotted line each  
20 independently represent a single or double bond, provided that when the



C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;

R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and

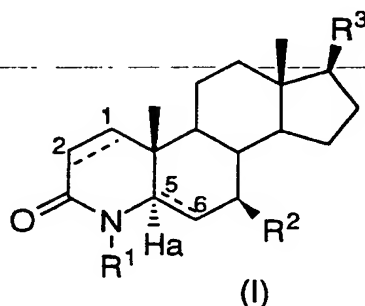
- 5 R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;

or a pharmaceutically acceptable salt, or stereoisomer thereof. The present invention further provides for a method for treating and  
 10 preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease as well as reducing the risk of fractures, both vertebral and nonvertebral, comprising administration of  
 15 therapeutically effective amount of compound of structural formula I to the subject. Further, the present invention provides for compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for inhibiting bone loss and treating or preventing osteoporosis and osteopenia.

20

## DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention is directed to a method for inhibiting bone loss in a subject in need thereof by administering to the subject an effective amount of a compound of  
 25 structural formula I:



wherein:

the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the

- C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;  
R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;  
R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and  
5 R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;

or a pharmaceutically acceptable salt, or stereoisomer thereof.

- Still a further aspect of the present invention is a method of  
10 preventing diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject in need thereof by administering  
15 an effective amount of a compound of structural formula I to the subject.

- Still another aspect of the present invention is the method of reducing the risk of diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and  
20 metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject at risk therefor by administering an effective amount of a compound of structural formula I to a subject.

- Yet a further aspect of the present invention is the method of treating diseases of the bone where inhibiting bone loss may be  
25 beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject in need thereof by administration of an effective amount of a compound of structural  
30 formula I to the subject.

Another aspect of the present invention is the use of a compound of structural formula I for the manufacture of a medicament useful to inhibit bone loss in a subject in need thereof. Still a further aspect of the present invention is the use of a compound of structural

formula I for the manufacture of a medicament useful to prevent diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. Still another aspect of the present invention is the use of a compound of structural formula I for the manufacture of a medicament useful to reduce the risk of diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject at risk therefor. Yet a further aspect of the present invention is the use of a compound of structural formula I for the manufacture of a medicament useful to treat diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

In one class of the instant invention are employed compounds of formula I wherein the C5-C6 bond is a single bond and H<sub>a</sub> is present.

In a sub-class of the compounds of this class are compounds wherein R<sup>2</sup> is methyl.

Compounds illustrating this sub-class are:

7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
4,7 $\beta$ ,20-trimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,

- 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 5 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 10 17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 15 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
 17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
 20 17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one, and  
 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one.

Compounds further illustrating this sub-class are:

- 25 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 30 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,

17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one, and  
 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one.

5

In a further subclass of the present invention are employed compounds wherein the C1-C2 bond is a double bond and R<sup>1</sup> is hydrogen.

Compounds illustrating this subclass include:

7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
 10 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 15 17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

20

In yet another subclass of this class of the present invention are employed compounds wherein R<sup>3</sup> is C<sub>3-6</sub> alkyl.

Compounds illustrating this sub-class are:

7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
 25 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 30 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 4,7 $\beta$ ,20-trimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,

- 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
5 17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
15 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one, and  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one.

20

Further illustrating this subclass are compounds wherein R<sup>2</sup> is methyl.

- In a further subclass of the present invention are employed compounds wherein the C1-C2 bond is a double bond, R<sup>1</sup> is hydrogen, R<sup>2</sup>  
25 is methyl, and R<sup>3</sup> is C<sub>3-6</sub> alkyl.

Compounds illustrating this subclass include:

- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
30 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,

17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one, and  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

Still further illustrating this subclass are compounds wherein R<sup>3</sup> is fully saturated.

5               Compounds illustrating this subclass include:

7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one, and  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

15

In another class of the present invention are employed compounds wherein the C5-C6 bond is a double bond and H<sub>a</sub> is absent.

When any variable (e.g., alkyl, R<sup>2</sup>, etc.) occurs more than one time in any constituent or in formula I, its definition on each  
20 occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the  
25 specified number of carbon atoms, e.g., methyl (Me), ethyl (Et), propyl, butyl, pentyl, and the isomers thereof such as isopropyl (i-Pr), isobutyl (i-Bu), secbutyl (s-Bu), tertbutyl (t-Bu), isopentane, etc.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts.

30               The term "pharmaceutically acceptable salt" is intended to include all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate,

mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, 5 polygalacturonate, gluconate, salicylate, glutamate, stearate, glycolylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoate, iodide, tosylate, isothionate, triethiodide, lactate, pantoate, valerate, and the like which can be used as a dosage 10 form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations.

The subject treated in the methods above is a mammal, preferably a human being, male or female, at risk of developing a disease where inhibiting bone loss may be beneficial, including: 15 osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. Alternatively the subject treated is a mammal, or preferably a human being, who has developed a disease where inhibiting bone loss may be 20 beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

A subject in need of the present invention may also be 25 identified as possessing bone fractures.

The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other 30 clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified 35 amounts.



By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

5 The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

10 The instant method of administering a compound of structural formula I is useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.
- 15 2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can alleviate the pain associated with osteolytic lesions and reduce the incidence and/or  
20 growth of those lesions.

These diseases include: osteoporosis (including estrogen deficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, periodontal  
25 disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany, as well as reducing the risk of fractures, both vertebral and nonvertebral.

The administration of the compound of structural formula I  
30 in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the patient in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors.  
35 The effective amount of an individual compound is determined, in the

final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment.

Generally, the daily dosage of the compound of structural formula I may be varied over a wide range from 0.01 to 1000 mg per adult human per day. Most preferably, dosages range from 0.1 to 50 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 3.0, 5.0, 6.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, when administered via intranasal routes, transdermal routes, by rectal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Formulations of the 5 $\alpha$ -reductase inhibitor employed in the present method for medical use comprise the compound of structural formula I together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient subject of the formulation.

The present invention, therefor further provides a pharmaceutical formulation comprising the compound of structural formula I together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, rectal, intravaginal, topical or parenteral (including subcutaneous, intramuscular and intravenous administration). Preferred are those suitable for oral administration.

The formulations may be presented in a unit dosage form and may be prepared by any of the methods known in the art of pharmacy. All methods include the step of bringing the active compound in association with a carrier which constitutes one or more  
5 ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound in association with a liquid carrier, a waxy solid carrier or a finely divided solid carrier, and then, if needed, shaping the product into desired dosage form.

Formulations of the present invention suitable for oral  
10 administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, or an emulsion.

15 A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents,  
20 disintegrating agents or coloring agents. Molded tablets may be made by molding in a suitable machine a mixture of the active compound, preferably in powdered form, with a suitable carrier.

Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and  
25 synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes and the like.

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Lubricants used in these dosage forms include, without limitation,  
sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include,  
30 without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral liquid forms, such as syrups or suspensions in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl cellulose  
35 and the like may be made by adding the active compound to the solution

or suspension. Additional dispersing agents which may be employed include glycerin and the like.

Formulations for rectal administration may be presented as a suppository with a conventional carrier, i.e., a base that is nontoxic and nonirritating to mucous membranes, compatible with the compound of structural formula I, and is stable in storage and does not bind or interfere with the release of the compound of structural formula I. Suitable bases include: cocoa butter (theobroma oil), polyethylene glycols (such as carbowax and polyglycols), glycol-surfactant combinations, polyoxyl 40 stearate, polyoxyethylene sorbitan fatty acid esters (such as Tween, Myrj, and Arlacel), glycerinated gelatin, and hydrogenated vegetable oils. When glycerinated gelatin suppositories are used, a preservative such as methylparaben or propylparaben may be employed.

Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations. See, e.g., EP 0 285 382.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethylene-oxide polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in

achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

- 5                   Formulations suitable for parenteral administration include formulations which comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution or suspension of a compound that is isotonic with the blood of the recipient subject.
- 10   Such formulations may contain distilled water, 5% dextrose in distilled water or saline and the active compound. Often it is useful to employ a pharmaceutically and pharmacologically acceptable acid addition salt of the active compound that has appropriate solubility for the solvents employed. Useful salts include the hydrochloride isothionate and
- 15   methanesulfonate salts. Useful formulations also comprise concentrated solutions or solids comprising the active compound which on dilution with an appropriate solvent give a solution suitable for parenteral administration.

- The compounds of the present invention may be coupled to a
- 20   class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

- 25               The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance vitamin D<sub>2</sub> and D<sub>3</sub> and hydroxylated derivatives, e.g. 1 $\alpha$ -hydroxy-vitamin D<sub>3</sub>, 1 $\alpha$ -hydroxy-vitamin D<sub>2</sub>, 1 $\alpha$ -25-dihydroxy-
- 30   vitamin D<sub>3</sub>, 1 $\alpha$ -25-dihydroxy-vitamin D<sub>2</sub>, dehydroepiandrosterone, calcitonin (human, porcine or salmon), mitramycin, sodium fluoride, estrogens, estrogen mimetics, including relaxafine and other compounds within the oxefine class, non-steroid antiinflammatory drugs, such as acetylsalicylic acid, indomethacin, naprosyn, and

timegadine, growth hormone secretagogues, growth hormone, growth hormone releasing hormone and insulin-like growth factor and bisphosphonates such as alendronate.

5 The composition and method of the present invention may further comprise a type 2  $5\alpha$ -reductase inhibitor or a dual  $5\alpha$ -reductase inhibitor. Preferred type 2  $5\alpha$ -reductase inhibitors for use in the present composition and method include: finasteride and epristeride. A preferred dual inhibitor is: 17 $\beta$ -N-(2,5-bis(trifluoromethyl))phenyl carbamoyl-4-aza- $5\alpha$ -androst-1-en-3-one.

10 One aspect of the present invention provides a method for inhibiting bone loss comprising administering to a mammal in need of treatment an effective amount of a compound of structural formula I.

Another aspect of the present invention provides the above-described method, and further comprises the coadministration of a bone antiresorptive agent and/or an anabolic agent and/or a  $5\alpha$ -reductase type 2 inhibitor and/or a dual  $5\alpha$ -reductase inhibitor. Bone antiresorptive agents are those agents which are known in the art to inhibit the resorption of bone and include, for example, estrogen in which estrogen includes steroidal compounds having estrogenic activity such as, for example, 17 $\beta$ -estradiol, estrone, conjugated estrogen (PREMARIN®), equine estrogen, 17 $\beta$ -ethynyl estradiol, and the like.

20 Bisphosphonate compounds may also be employed in combination with the compound of structural formula I of the present invention include:

- 25 (a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,  
(b) N-methyl-4-amino-hydroxybutylidene-1,1-bisphosphonic acid,  
(c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-bisphosphonic acid,  
30 (d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,  
(e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid,  
(f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid,

(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid,  
and

(h) 4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine,  
and their pharmaceutically acceptable salts. Especially preferred is  
5 alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid  
monosodium salt, trihydrate. Methods for the preparation of  
bisphosphonic acids may be found in, e.g., U.S. Patent No. 3,251,907;  
U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No.  
3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S.  
10 Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No.  
4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S.  
Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654;  
U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,077. In particular,  
methods for the preparation of 4-amino-1-hydroxybutylidene-1,1-  
15 bisphosphonic acid monosodium salt trihydrate may be found in U.S.  
Patent No. 4,407,761 and U.S. Patent No. 4,621,077.

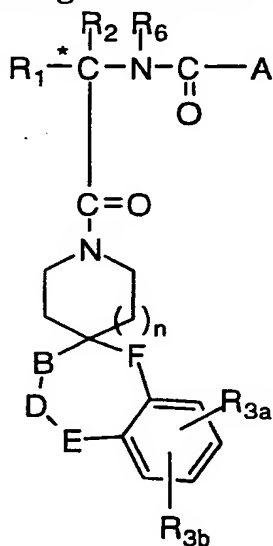
Still further, antiestrogenic compounds such as raloxifene  
(see, e.g., U.S. Pat. No. 5,393,763) clomiphene, zuclophene,  
enclomiphene, nafoxidene, CI-680, CI-628, CN-55,945-27, Mer-25, U-11,  
20 555A, U-100A, and salts thereof, and the like (see, e.g., U.S. Pat. Nos.  
4,729,999 and 4,894,373) may be employed in combination with the  
compound of structural formula I in the methods and compositions of  
the present invention.

Bone anabolic agents are those agents which are known in  
25 the art to build bone by increasing the production of the bone protein  
matrix. Such anabolic agents include, for example, the various forms of  
parathyroid hormone (PTH) such as naturally occurring PTH (1-84),  
PTH (1-34), analogs thereof, growth hormone secretagogues, growth  
hormone, growth hormone releasing hormone and insulin-like growth  
30 factor and the like.

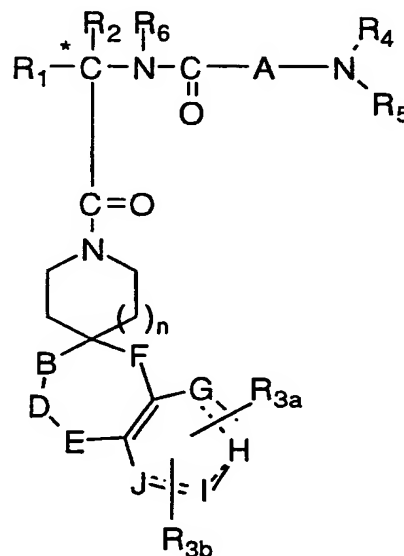
Representative growth hormone secretagogues are  
disclosed in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S.  
Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No.  
5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S.  
35 Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144;

U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; Science, **260**, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., **28**, 177-186 (1993); Bioorg. Med. Chem. Ltrs., **4**(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA **92**, 7001-7005 (July 1995).

Representative growth hormone secretagogues are disclosed in U.S. Patent No. 5,536,716 as spiro compounds of the following structural Formulas I and II:



Formula I



Formula II

wherein the various substituents are as defined in U.S. Patent No. 5,536,716.



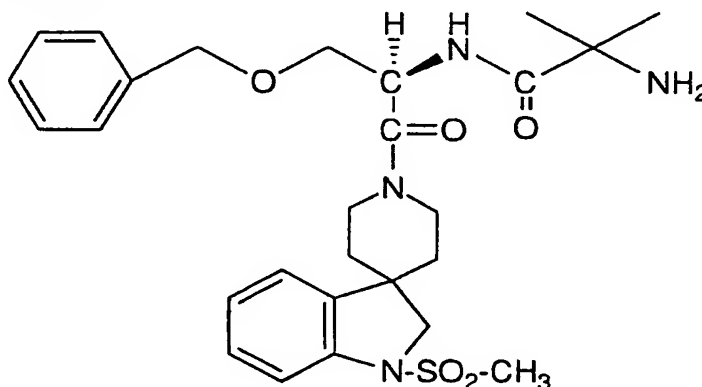
Preferred growth hormone secretagogues for use in the present invention include:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and

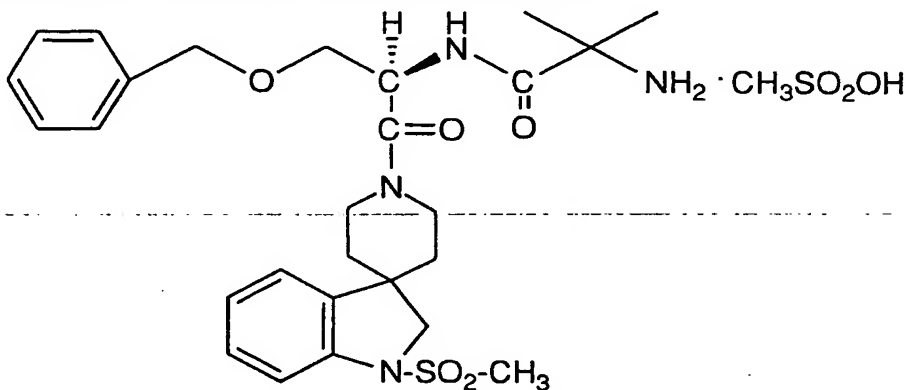
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

10

Especially preferred growth hormone secretagogues specifically include:



and pharmaceutically acceptable salts thereof; and



15

The preparation of growth hormone secretagogues is well known in the literature. Full descriptions of the preparation of the growth hormone secretagogues is found in e.g., U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No.

5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

Daily dosage ranges for bone antiresorptive and anabolic agents and 5 $\alpha$ -reductase type 2 inhibitors and dual 5 $\alpha$ -reductase inhibitors are those which are known in the art.

In particular, when a bisphosphonic acid is employed, dosages of 2.5 to 100 mg/day (measured as the free acid) are appropriate for treatment, more preferably 5 to 20 mg/day, especially about 10 mg/day. Prophylactically, doses of about 2.5 to about 10 mg/day and especially about 5 mg/day should be employed.

In particular, when a type 2 5 $\alpha$ -reductase inhibitor or a dual 5 $\alpha$ -reductase inhibitor is employed, dosages of 0.01 to 10 mg per adult human per day are appropriate for treatment, more preferably 1 to 5 mg/day especially preferred is about 5 mg/day.

The compounds of the methods of the present invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal, and such compounds are preferably formulated prior to administration. Therefore, another embodiment of the present invention

is a pharmaceutical formulation comprising an effective amount of a compound of structural formula I or a pharmaceutically acceptable salt thereof, a bone antiresorptive or anabolic agent or a type 2 5 $\alpha$ -reductase inhibitor or a dual 5 $\alpha$ -reductase inhibitor, and a pharmaceutically acceptable carrier, diluent or excipient therefor.

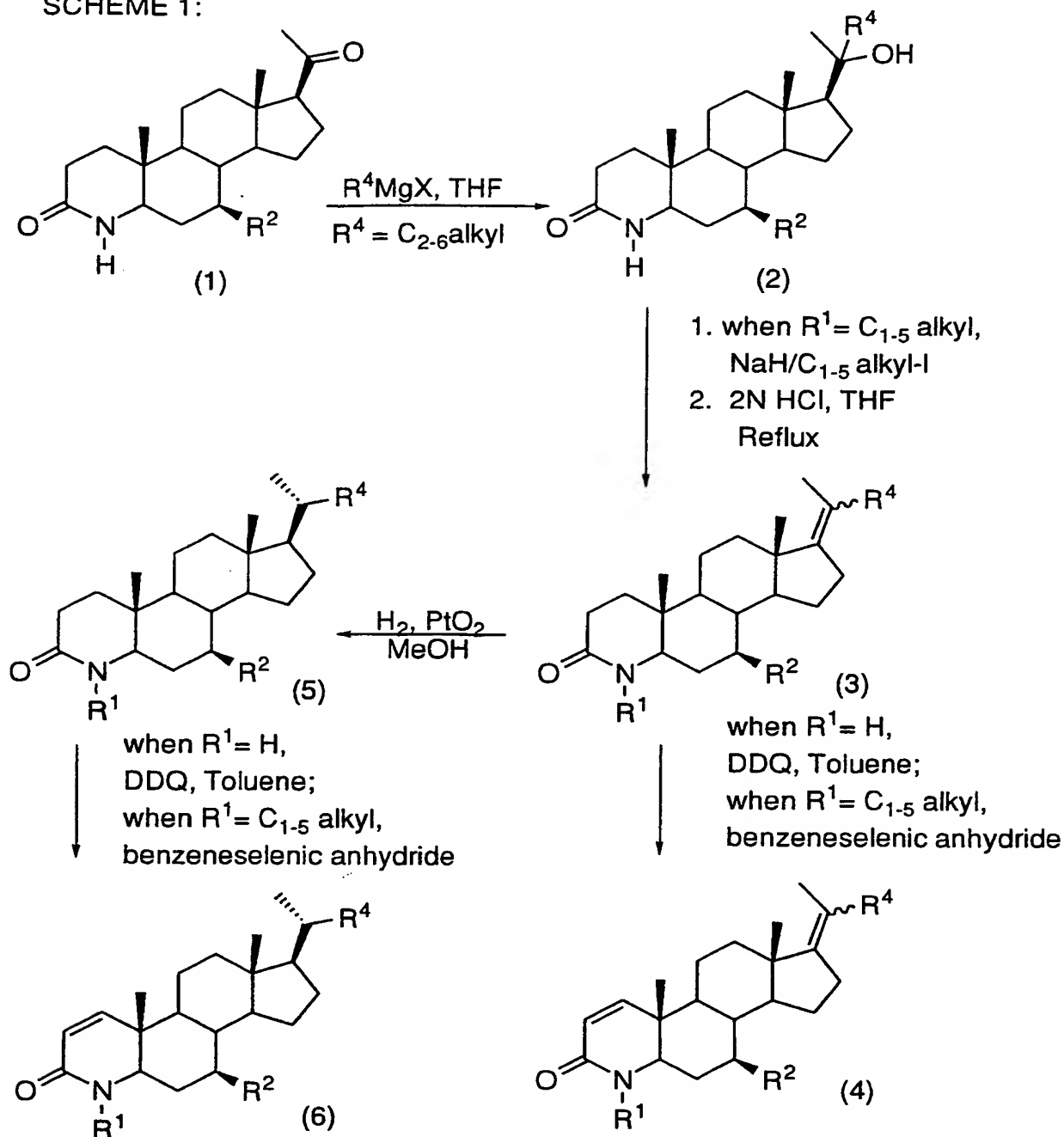
In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating or preventing bone loss includes in principle any combination with any pharmaceutical composition useful for inhibiting bone loss or building new bone.

The 5 $\alpha$ -reductase type 2 inhibitor finasteride that may employed this invention can be prepared as described in U.S. 4,760,071.

The compounds of the present invention can be prepared readily according to the following Schemes and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The compounds of this invention can be prepared as shown in Scheme 1.

SCHEME 1:



- Starting with commercially available pregnenolone acetate, the appropriately 7-substituted derivative is prepared according to the procedures of PCT publication WO 93/23420 and to produce (1), the 7 $\beta$ -alkyl-substituted pregnenolone acetate. Treating (1) with the
- 5
- appropriate C<sub>2-6</sub>alkyl Grignard in tetrahydrofuran (THF), produces the

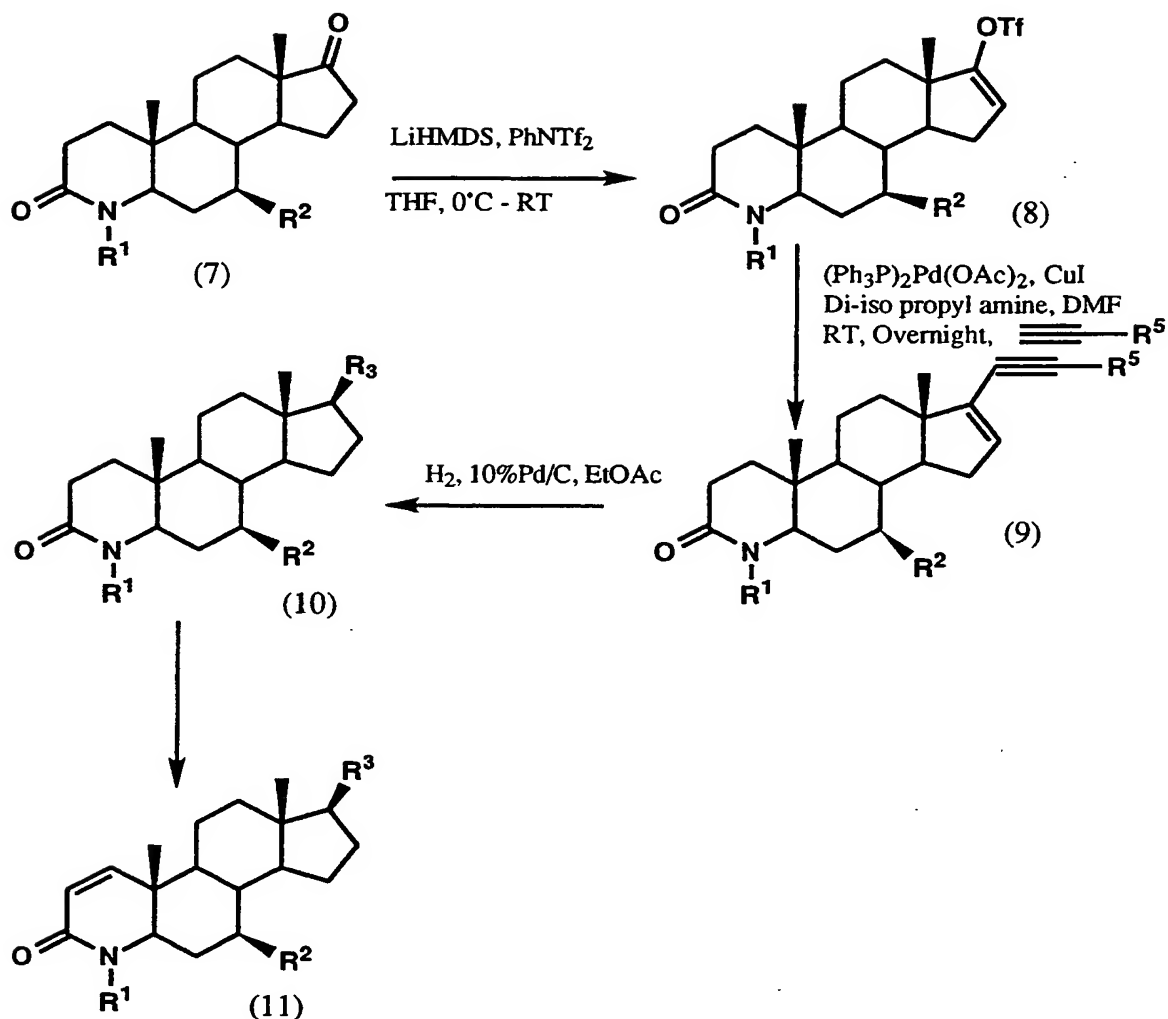
tertiary carbinol (2). The tertiary carbinol (2) may be alkylated at the 4-position by treatment with sodium hydride and the appropriate C<sub>1-5</sub>alkyl iodide in a polar aprotic solvent such as THF or dimethylformamide (DMF). The 4-NH or 4-N-alkyl compound is then dehydrated in the  
5 presence of acid, for example, HCl or acetic acid, in a solvent such as THF or alcohol to produce the 17-ene (3). The 17-ene (3), in turn, may be dehydrogenated to form the 1,17-diene (4) by treatment with DDQ in toluene or benzeneselenic anhydride in chlorobenzene, or other known methods, for example as described in U.S. 5,084,574 and 5,021,571. DDQ  
10 is preferred for 4-NH compounds and benzeneselenic anhydride is preferred for 4-N-alkyl compounds.

Alternatively, the 17-ene (3) may be hydrogenated in the presence of a hydrogenation catalyst, for example PtO<sub>2</sub>, Pd/C, rhodium on alumina, preferably PtO<sub>2</sub>, in an appropriate solvent such as an  
15 alcohol or acetic acid, preferably methanol, to form the 17-alkyl derivative (5). The 17-alkyl derivative (5), in turn, may be dehydrogenated to form the 1-ene (6) by treatment with DDQ in toluene or benzeneselenic anhydride in chlorobenzene, as described above.

The desired 4-N-alkyl substitution may be effected as  
20 described previously by treating (2) with the appropriate alkyl iodide, or alternative, the procedure may be carried through with the 4-NH compound, and following after the desired 17-substitution and optional insertion of the 1,2-double bond, the 4-NH compound may be alkylated to the desired 4-N-alkyl compound.

25 Processes for inserting the 1,2-double bond in a 3-oxo-4-azasteroid are described in U.S. Patents 5,084,574 and 5,021,571. The formation of a 7- $\beta$  bond is described in U.S. Patents 4,220,775 5,237,064.

SCHEME 2



Alternatively, the compounds of the present invention may be prepared according to the procedures of Scheme 2. Compound (7), obtained according to procedures in WO 93/23420, is treated with N-phenyl trifluoro methane sulfonamide in a base such as lithium hexamethyldisilazide in THF to form the enol triflate (8). The enol triflate (8) is converted to the desired enyne (9) by treatment with di(triphenylphosphine)palladium diacetate or other appropriate Pd<sub>0</sub> catalyst with a catalytic amount of cuprous iodide and a mild base such as diisopropylamine or triethylamine in DMF with the appropriate alkyne. The enyne (9) is hydrogenated to produce the 17-alkyl derivative

(10) by treating with H<sub>2</sub> in the presence of 10% Pd/C in an alcoholic or ethyl acetate solvent, preferably ethyl acetate. Insertion of the 1,2-double bond, if desired is accomplished as described in Scheme 1 to produce the 17-alkyl-1-ene (11).

5           The following examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Furthermore, examples are not to be construed as forming the only methods and compositions that are considered as the invention. Those skilled in the art will readily understand that known variations of  
10 the conditions, processes, methods and compositions of the following preparative procedures can be used.

#### EXAMPLE 1

##### 7 $\beta$ ,20-Dimethyl-4-aza-5 $\alpha$ -pregna-17-en-3-one

15   Step 1:     3-Acetoxy-pregn-5-en-20-ol

Sodium borohydride (21 gm) was added to a solution of pregnenolone acetate (100 g, 0.28 mol) in absolute ethanol (1 L) and methylene chloride (0.4 L) at -10°C. After stirring overnight at 4°C, another amount of sodium borohydride (10.5 gm) was added and the  
20 reaction stirred at room temperature overnight. The reaction mixture was quenched by pouring into 5% sodium phosphate monobasic (2 L) and extracted with methylene chloride. The organic extracts were dried over anhydrous magnesium sulfate and filtered through a pad of anhydrous sodium sulfate. The solvent was removed by rotoevaporation to give the  
25 title compound.

Step 2:     3-Acetoxy-20-*tert*-butyldimethylsilyloxy-pregn-5-ene

Imidazole (203.7 gm, 2.28 mol) was added to a stirred suspension of 3-acetoxy-pregn-5-en-20-ol (361 gm, 1 mol, product of Step  
30 1) in dimethylformamide (3.7 L). *t*-Butyldimethylsilyl chloride (228.9 mg, 1.52 mol) was added over a 10-15 min period. The mixture was stirred at room temperature for 3 days. The dimethylformamide was removed by decantation and methanol (50 mL) was added to it. Water (4 L) was added and the solution extracted with ethyl acetate (2 x 4 L). The

precipitate remaining behind after decantation was dissolved in ethyl acetate and added to the above ethyl acetate extracts. The combined solvent extracts were washed with water, saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation and the product purified by column chromatography on silica gel eluted with 2:1 hexane-methylene chloride followed by 1:1 hexane-methylene chloride. The title compound was isolated as a mixture of 20 $\alpha$ - and  $\beta$ -isomers.

10 Step 3: 3-Acetoxy-20-*tert*-butyldimethylsilyloxy-pregn-5-en-7-one  
To a solution of 3-acetoxy-20-*tert*-butyldimethylsilyloxy-pregn-5-ene (337 gm, 0.71 mol, product of Step 2) in methyl ethyl ketone (4 L) was added N-hydroxyphthalimide (115.8 gm, 0.71 mol) and dibenzoyl peroxide (1.1 gm, 4.4 mmol). Air was bubbled through the reaction as the reaction was refluxed for 7.5 hr. Additional N-hydroxyphthalimide (9 gm) and dibenzoyl peroxide (0.1 gm) were added and reflux continued for 5 hr. The solvent was removed by rotoevaporation and methylene chloride (0.7 L) was added and warmed to 40°C. Upon cooling to room temperature, the suspension was filtered and the filtrate washed with methylene chloride (0.2 L). The filtrate was rotoevaporated and treated with pyridine (1.35 L) and acetic anhydride (135 mL). After stirring overnight, the solvent was removed by rotoevaporation and the dark orange oil dissolved in methanol (0.6 L). The mixture was heated to 50°C and then cooled to room temperature. The solution was allowed to stand for 3 days and then cooled in an ice bath. The precipitate was filtered, washed with methanol, and dried to yield the title compound. The filtrate was rotoevaporated to a dry gum to yield the crude product.

30 Step 4: 20-*tert*-Butyldimethylsilyloxy-7-methyl-pregn-5-ene-3,7-diol

A solution of 3-acetoxy-20-*tert*-butyldimethylsilyloxy-pregn-5-en-7-one (279 gm, 0.57 mol, product of Step 3) in tetrahydrofuran (5.6 L) was cooled to 4°C. A 3M solution of methyl magnesium chloride in tetrahydrofuran (1.037 L, 3.1 mol) was added at such a rate as to keep the temperature  $\leq 0^\circ\text{C}$ . The ice bath was removed and the reaction allowed



to warm to room temperature overnight. The reaction was cooled in an ice bath and quenched with a 20% solution of ammonium chloride (3 L). The organic layer was removed and the aqueous layer extracted with ethyl acetate. The organic layers were combined, washed with saturated salt solution, and dried over anhydrous magnesium sulfate. The solution was filtered through a pad of anhydrous sodium sulfate and the solvent removed by rotoevaporation to yield the title compound.

Step 5: 20-*tert*-Butyldimethylsilyloxy-7-methyl-pregn-4,6-dien-3-one

A solution of 20-*tert*-butyldimethylsilyloxy-7-methyl-pregn-5-ene-3,7-diol (298 gm, 0.59 mol, product of Step 4) in toluene (3 L) and cyclohexanone (1.03 L) was azeotroped to remove 750 mL of solvent. A solution of aluminum isopropoxide (121 gm) in toluene (620 mL) was added and the solution azeotroped to remove another 650 mL of solvent. A reflux condenser was added and the solution refluxed overnight. The solution was cooled to 40°C and Supercell™ (125 gm) and water (125 mL) were added. After stirring for 10 min, the mixture was filtered and the solids washed with toluene (550 mL). The solvent was removed by rotoevaporation to yield a orange liquid which was purified by column chromatography on silica gel eluted with hexane, followed by 5-10% ethyl acetate in hexanes. The title compound was isolated as a mixture of 20 $\alpha$ - and 20 $\beta$ -isomers.

Step 6: 20-*tert*-Butyldimethylsilyloxy-7 $\beta$ -methyl-pregn-4-en-3-one

A slurry of 5% palladium on carbon (7.12 gm) and benzyl alcohol (213 mL) in heptane (356 mL) was refluxed for 20 min. The mixture was cooled to 80°C and a solution of 20-*tert*-butyldimethylsilyloxy-7-methyl-pregn-4,6-dien-3-one (71.2 gm, 0.16 mol, product of Step 5) in heptane (427 mL) was added. The slurry was refluxed for 9.5 h. The reaction was cooled to room temperature and filtered through SOLKA FLOK filter aid which was subsequently washed with hexane. The filtrate was extracted with acetonitrile which was subsequently back-extracted with hexane. The heptane and hexane extracts were

combined, washed with saturated sodium sulfate and saturated salt solutions, and dried over anhydrous magnesium sulfate. The solution was filtered through a pad of anhydrous sodium sulfate and the solvent removed by rotoevaporation. The title compound was purified by column chromatography on silica gel eluted with 7% ethyl acetate in hexanes.

Step 7: 20-*tert*-Butyldimethylsilyloxy-7 $\beta$ -methyl-5-oxo-A-nor-3,5-secopregnan-3-oic acid

To a solution of 20-*tert*-butyldimethylsilyloxy-7 $\beta$ -methyl-pregn-4-en-3-one (73.57 gm, 0.165 mol, product of Step 6) in *tert*-butanol (0.96 L) was added a solution of sodium carbonate (25.8 gm) in water (120 mL). The mixture was heated to 80°C with stirring. A warm solution of sodium periodate (244 gm) and potassium permanganate (1.91 gm) in water (0.96 L) was slowly added and then the reaction refluxed for 2 h. The reaction was cooled to room temperature and filtered through a pad of SuperCell™. The filter cake was washed with water (2 x 190 mL). The combined filtrates were rotoevaporated to remove the *tert*-butanol and washed with methylene chloride. The aqueous solution was acidified to pH ~ 3 with 2N hydrochloric acid and extracted with methylene chloride (3x). The organic extracts were combined, washed with 5% sodium bisulfite solution and saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation to yield the title compound as a white foam.

Step 8: 20-*tert*-Butyldimethylsilyloxy-7 $\beta$ -methyl-4-azapregn-5-ene

To a solution of 20-*tert*-butyldimethylsilyloxy-7 $\beta$ -methyl-5-oxo-A-nor-3,5-secopregnan-3-oic acid (26 gm., 56 mmol, product of Step 7) in ethylene glycol (500 mL) under nitrogen was added anhydrous ammonium acetate (50 gm). The mixture was heated at 180°C for 5 h, cooled to room temperature, and diluted with water (3.5 L). After stirring for 1 hr, the solid was filtered and the aqueous layer was extracted with methylene chloride (500 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent removed by rotoevaporation. The residue was combined with the filtered solid and dried in a vacuum oven overnight to give the title compound.

Step 9: 20-*tert*-Butyldimethylsilyloxy-7 $\beta$ -methyl-5 $\alpha$ -4-azapregnan-5-ene

To a solution of 20-*tert*-butyldimethylsilyloxy-7 $\beta$ -methyl-4-azapregnan-5-ene (23.9 g, 53.6 mmol, product of Step 8) in acetic acid (250 mL) was added platinum oxide (1.8 gm). The mixture was stirred overnight under hydrogen (1 atmosphere). The reaction mixture was filtered through a pad of Celite™ filter aid (trademark for diatomaceous earth) and the filtrate was coevaporated with toluene (3 x 500 mL) to remove all of the acetic acid. The residue was dissolved in chloroform and filtered again through a pad of Celite™ filter aid to remove residual catalyst. The solvent was removed by roto-evaporation to yield the title compound which was taken directly on to the next step without any further purification.

Step 10: 20-Hydroxy-7 $\beta$ -methyl-5 $\alpha$ -4-azapregnan-3-one

To a slurry of crude 20-*tert*-butyldimethylsilyloxy-7 $\beta$ -methyl-5 $\alpha$ -4-azapregnan-5-ene (25.2 g, product of Step 9) in acetonitrile (300 mL) was added an aqueous solution of hydrofluoric acid (12 mL). After stirring for 8 hr at room temperature, the reaction mixture was cooled to 0°C and saturated sodium bicarbonate solution was slowly added. The mixture was extracted with methylene chloride (3 x 500 mL) and the combined extracts washed with water, saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation to give the title compound which was used without purification in the subsequent reaction.

Step 11: 7 $\beta$ -Methyl-5 $\alpha$ -4-azapregnan-3,20-dione

To a stirred solution of 20-hydroxy-7 $\beta$ -methyl-5 $\alpha$ -4-azapregnan-3-one (22.3 gms, 67 mmol, product of Step 10) in dry methylene chloride under nitrogen (110 mL) was added 4-methylmorpholine N-oxide (11.8 gms, 100 mmol) followed by 4Å molecular sieves (33 gm). To this mixture was added tetrapropylammonium perruthenate (1.2 gm). After stirring at room temperature for 4 h, the reaction mixture was poured through pad of silica gel in a 300 mL sintered glass funnel which was subsequently eluted with 4:1 ethyl

acetate/methylene chloride (5 L). The solvent was removed by rotoevaporation and the title compound recrystallized.

Step 12: 20-Hydroxy-7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

5 To a solution of 7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnane-3,20-dione (1.24 g., 3.73 mmol., product of Step 11) in tetrahydrofuran (20 mL.) was added methylmagnesiumbromide in diethyl ether (3.73 mL., 11.2 mmol) at room temperature. The reaction was stirred for 45 minutes under a nitrogen atmosphere and then quenched with saturated ammonium  
10 chloride solution and diluted with ethyl acetate (500 mL.). The organic phase was washed with water (500 mL, x 2) and brine solution (300 mL.). It was dried over sodium sulfate, filtered and the solvent evaporated in vacuo to give a white foam. The foam was flash chromatographed on silica gel using methanol in methylene chloride (1:19) as the mobile  
15 phase to yield a white foam. The foam was then recrystallized in methylene chloride and hexane (1:4) to yield the titled compound as white crystals. R<sub>f</sub> = 0.35, 5% methanol : methylene chloride. 400 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>) :  $\delta$  0.82 (s, 3H); 0.87 (s, 3H); 1.16(s, 3H); 1.27 (s, 3H); 3.04 (dd, 1H).

20

Step 13: 7 $\beta$ ,20-Dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one

A mixture of 20-Hydroxy-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one (0.810 g., 2.35 mmol, product of Step 12), 2M hydrochloric acid (35 mL.) and tetrahydrofuran (THF, 35 mL) was refluxed at 70°C for 3 hours.  
25 THF was then evaporated in vacuo and the aqueous phase was basified using 2.5 M sodium hydroxide. The aqueous phase was then extracted with methylene chloride (200 mL) three times. The organic phases were combined and washed water (500 mL.) and brine (300 mL.). The organic phase was then dried with sodium sulfate, filtered and the solvent  
30 evaporated in vacuo to give a yellow oil. The oil was recrystallized in methylene chloride and hexane (1:3) to give a yellow solid.

EXAMPLE 2

7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

To a solution of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-17-en-3-one (730 mg., 2.22 mmol, the product of Example 1) and methanol (40 mL) was added platinum oxide (250 mg). This mixture was stirred under a hydrogen atmosphere overnight. It was then filtered through Celite™ diatomaceous earth and the solvent was removed under vacuum. The crude residue was chromatographed using 10 % 2-propanol in hexane as the mobile phase to yield the titled compound as a white solid. 400 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>) :  $\delta$  0.66 (s, 3H); 0.83 (d, 3H); 0.85 (s, 3H); 0.91 (d, 3H); 0.99 (d, 3H); 3.05 (dd, 1H). Mass spec. = 332 (M+1)

### EXAMPLE 3

#### 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one

To a solution of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-3-one (500 mg., 1.51 mmol, the product of Example 2) in dry toluene (15 mL.) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (410 mg, 1.81 mmol), bis(trimethyl silyl)trifluoroacetamide (1.6 mL, 6.04 mmol) and triflic acid (0.00625 mL., 0.068 mmol). The mixture was stirred under nitrogen atmosphere overnight, followed by addition of methyl acetoacetate 90.032 mL., 0.30 mmol). The mixture was then refluxed overnight. The reaction mixture was poured into water (100 mL) containing sodium bicarbonate (800 mg.) and sodium sulfite (300 mg) and extracted with methylene chloride (3 x 100 mL). The organic phases were combined and washed with water (200 mL) and brine (100 mL). The organic phase was dried over sodium sulfate, filtered and the solvent evaporated in vacuo. The residue was purified by flash chromatography on silica gel eluted with 15% acetone in methylene chloride and recrystallization methyl ethyl ketone (MEK) to yield titled compound. 400 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>) :  $\delta$  0.67 (s, 3H); 0.82 (d, 3H); 0.89 (s, 3H); 0.92 (d, 3H); 1.01 (d, 3H); 3.34 (dd, 1H); 5.78 (dd, 1H); 6.78 (d, 1H). Mass spec. = 330 (M+1)

### EXAMPLE 4

#### 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one

The titled compound was synthesized in the same fashion as 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-ene-3-one, starting with 7 $\beta$ ,20-

dimethyl-4-aza-5 $\alpha$ -pregna-17-en-3-one with the exception it was purified by recrystallization in ethyl acetate. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.85 (s, 3H); 0.90 (s, 3H); 1.04 (d, 3H); 1.54 (s, 3H); 1.68 (s, 3H); 3.34 (dd, 1H); 5.78 (dd, 1H); 6.78 (d, 1H). Mass spec. = 328 (M+1)

5

#### EXAMPLE 5

##### 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one

Step 1: Preparation of 20-Ethyl-20-hydroxy-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one

10 The titled compound was synthesized in a similar fashion to 20-Hydroxy-7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnane-3-one using 3M ethylmagnesium bromide in diethyl ether in place of the methylmagnesium bromide. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.82 (s, 3H); 0.84 (t, 3H); 0.86 (s, 3H); 0.99 (d, 3H); 1.23 (s, 3H); 3.03 (dd, 1H). Mass  
15 spec. = 343 (M-18)

Step 2: Preparation of 20-Ethyl-20-hydroxy-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

20 To a slurry of sodium hydride (8.0 mg., 0.2 mmol) and 20-Ethyl-20-hydroxy-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one (63.0 mg., 0.17 mmol, product of Step 1) in tetrahydrofuran was added methyl iodide (15.0 mL., 2.55 mmol). The solution was allowed to stir under a nitrogen atmosphere at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate (2 x 100 mL.). The organic  
25 phase was washed with water (100 mL) and brine ( 100 mL) and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue purified via flash chromatography on silica gel eluding with 10 % acetone in methylene chloride to yield the titled compound as a white foam. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.81-0.84 (t, 3H); .083 (s, 3H); 0.85 (s,  
30 3H); 1.03 (d, 3H); 1.22 (s, 3H); 2.9 (s, 3H); 2.99 (dd, 1H). Mass spec. = 375 (M+)

Step 3: 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one

The titled compound was synthesized in a similar fashion to 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-17-ene-3-one and taken forward without any purification.

5

EXAMPLE 620-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

The titled compound was synthesized in a similar fashion to 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnane-3-one, starting with the product of Example 5. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.64 (d, 3H); 0.79 (d, 3H); 0.83 (s, 3H); 0.88 (d, 3H); 1.04 (d, 3H); 2.89 (s, 3H); 3.0 (dd, 1H). Mass spec. = 359 (M+)

10

EXAMPLE 720-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

15 Step 1: 20-Allyl-20-hydroxy-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one

The titled compound was synthesized in a similar fashion to 20-Hydroxy-7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one using 2M allylmagnesium chloride in tetrahydrofuran in place of the methylmagnesium bromide. No further purification was done prior to the following step.

20

Step 2: 20-Allyl-20-hydroxy-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

The titled compound was synthesized in a fashion similar to 20-ethyl-20-Hydroxy-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.82 (s, 3H); 0.85 (s, 3H); 1.03 (d, 3H); 1.26 (s, 3H); 2.89 (s, 3H); 3.00 (dd, 1H); 5.05 (dd, 2H); 5.78 (m, 1H).

25

Step 3: 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one

30 A slurry of 20-allyl-20-Hydroxy-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one (29.0 mg., 0.075 mmol), 10% palladium on carbon (5.0 mg.) and a mixture of ethyl acetate-ethanol (5.0 mL., 1:1) was stirred for 48 hours under a hydrogen atmosphere at room temperature. The reaction was then filtered through Celite<sup>TM</sup> and the solvent evaporated in vacuo. The residue was purified via HPLC on a Waters 19 x 300 mm 8m

35

silica Nova Pak column using a 5 to 10 % 2-propanol/hexane linear gradient at a 20 mL. per minute flow rate to yield the titled compound. 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  0.65 (s, 3H); 0.80 (m, 9H); 1.02 (d, 3H); 2.89 (s, 3H); 3.00 (dd, 1H). Mass spec. = 373 (M+)

5

#### EXAMPLE 8

##### Effect of $7\beta,20$ -dimethyl-4-aza- $5\alpha$ -pregna-1-en-3-one on bone mineral density in men

Young men are entered into the study and are randomized to treatment with 5 mg/day  $7\beta,20$ -dimethyl-4-aza- $5\alpha$ -pregna-1-en-3-one or placebo for 48 weeks. Lumbar spine bone mineral density, measured by dual energy X-ray absorptometry (DXA), and indices of bone metabolism, including Cross-Linked N-Telopeptides of Type 1 Collagen (NTX) and Bone-Specific Alkaline Phosphatase (BSAP) are measured at weeks 12, 24, 36 and 48.

15

#### EXAMPLE 9

Older men are enrolled in a 4-year, double-blind, placebo-controlled trial and are randomly assigned to treatment with a compound of structural formula I or placebo. Bone density is measured at baseline, years 2, 3, and 4. Biochemical markers of bone are also measured at these time points.

20

#### EXAMPLE 10

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 3 mg of  $7\beta,20$ -dimethyl-4-aza- $5\alpha$ -pregna-1-en-3-one is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

30

#### EXAMPLE 11

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 0.5 mg of a compound of structural formula



I is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

#### EXAMPLE 12

##### 5 Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 2.5 mg of a compound of structural formula I is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

10

#### EXAMPLE 13

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 6 mg of a compound of structural formula I is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

15

#### EXAMPLE 14

##### Transdermal Patch Formulation

20

<u>Ingredient</u>	<u>Amount</u>
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one	40 g
Silicone fluid	45 g
Colloidal silicone dioxide	2.5 g

The silicone fluid and 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut into 10 cm<sup>2</sup> patches. For 100 Patches.

25

30

EXAMPLE 15Suppository

<u>Ingredient</u>	<u>Amount</u>
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one	25 g
Polyethylene glycol 1000	1481 g
Polyethylene glycol 4000	494 g

- 5 The polyethylene glycol 1000 and polyethylene glycol 4000 are mixed and melted. The 5 $\alpha$ -reductase type 1 inhibitor is mixed into the molten mixture, poured into molds and allowed to cool. For 1000 suppositories.

EXAMPLE 1610 Injectable solution

<u>Ingredient</u>	<u>Amount</u>
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one	5 g
Buffering agents	q.s.
Propylene glycol	400 mg
Water for injection	600 mL

- 15 The 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving. For 1000 Ampules.

EXAMPLE 17Injectable solution

20

<u>Ingredient</u>	<u>Amount</u>
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one	5 g
Buffering agents	q.s.
Magnesium sulfate heptahydrate	100 mg
Water for injection	880 mL

The 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one, magnesium sulfate heptahydrate and buffering agents are dissolved in the water for injection with stirring, and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving. For 1000 Ampules.

5

#### EXAMPLE 18

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 3 mg of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one and 2.5 mg of alendronate monosodium salt trihydrate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

15

#### EXAMPLE 19

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 0.5 mg of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one and 10.0 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

20

#### EXAMPLE 20

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 2.5 mg of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one and 5.0 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

30

#### EXAMPLE 21

##### Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 6 mg of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one and 2.5 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with  
5 sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

#### EXAMPLE 22

##### Transdermal Patch Formulation

10

<u>Ingredient</u>	<u>Amount</u>
alendronate	50 g
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one	40 g
Silicone fluid	45 g
Colloidal silicone dioxide	2.5 g

The silicone fluid alendronate and 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregna-1-en-3-one are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat  
15 sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut  
20 into 10 cm<sup>2</sup> patches. For 100 Patches.

#### EXAMPLE 23

##### Preparation of Human Prostatic and Scalp 5 $\alpha$ -Reductases

Samples of human tissue were pulverized using a freezer  
25 mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500 x g for 15 min.  
30 The crude nuclear pellet was washed two times and resuspended in two

volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5

#### EXAMPLE 24

##### 5 $\alpha$ -Reductase Assay

The reaction mixture for the type 1 5 $\alpha$ -reductase contained 40 mM potassium phosphate, pH 6.5, 5 mM [7-<sup>3</sup>H]-testosterone, 1 mM dithiothreitol and 500  $\mu$ M NADPH in a final volume of 100  $\mu$ L. The reaction mixture for the type 2 5 $\alpha$ -reductase contained 40 mM sodium citrate, pH 5.5, 0.3 mM [7-<sup>3</sup>H]-testosterone, 1 mM dithiothreitol and 500  $\mu$ M NADPH in a final volume of 100  $\mu$ L. Typically, the assay was initiated by the addition of 50-100  $\mu$ g prostatic homogenate or 75-200  $\mu$ g scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250  $\mu$ L of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10  $\mu$ g each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman Partisil 5 silica column equilibrated in 1 ml/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655 $\alpha$  Autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

##### Inhibition Studies

Compounds were dissolved in 100% ethanol. The compound to be tested was pre-incubated with the enzyme (either 5 $\alpha$ -reductase type 1 or 2) prior to initiation by addition of substrate testosterone. IC<sub>50</sub>

values represent the concentration of inhibitor required to decrease enzyme conversion of testosterone to dihydrotestosterone by 50% of the control. IC<sub>50</sub> values were determined using a 6 point titration where the concentration of the inhibitor was varied from 0.1 to 1000 nM.

- 5 Representative compounds of this invention were tested in the above described assay for 5 $\alpha$ -reductase type 1 and type 2 inhibition.

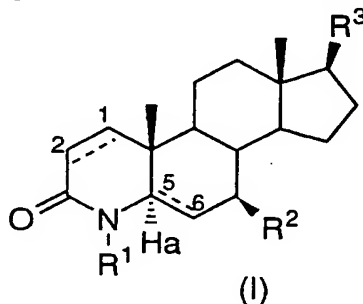
A compound referred to herein as a 5 $\alpha$ -reductase 2 inhibitor is a compound that shows inhibition of the 5 $\alpha$ -reductase 2 isozyme in the above-described assay, having an IC<sub>50</sub> value of about or under 100 nM.

- 10 The compounds are tested in the above-described assay for 5 $\alpha$ -reductase type 1 and type 2 inhibition, and were found to have IC<sub>50</sub> values under about 100 nM for inhibition of the type 1 isozyme. Compounds found to have IC<sub>50</sub> values of under about 50 nM for inhibition of the type 1 isozyme are called type 1 inhibitors. Compounds  
15 called "dual inhibitors" additionally had IC<sub>50</sub>'s under about 200 nM for inhibition of the type 2 isozyme.

- While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the  
20 art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of  
25 the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and  
30 such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

## WHAT IS CLAIMED IS:

1. A method of inhibiting bone loss in a subject in need of such treatment comprising administration to the subject of an effective amount of a compound of structural formula I:



wherein:

- the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;
- R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;
- R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and
- R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;
- or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein the compound of structural formula I is selected from:
- 7β,20-dimethyl-4-aza-5α-pregn-17-en-3-one,
- 7β,20-dimethyl-4-aza-5α-pregn-1,17-dien-3-one,
- 20-ethyl-4,7β-dimethyl-4-aza-5α-pregn-17-en-3-one,
- 20-ethyl-4,7β-dimethyl-4-aza-5α-pregnan-3-one ,
- 7β,20-dimethyl-4-aza-5α-pregnan-3-one,
- 7β,20-dimethyl-4-aza-5α-pregn-1-en-3-one,
- 20-ethyl-4,7β-dimethyl-4-aza-5α-pregnan-3-one,
- 20-propyl-4,7β-dimethyl-4-aza-5α-pregnan-3-one,
- 20-ethyl-4,7β-dimethyl-4-aza-5α-pregn-1-en-3-one,
- 4,7β,20-trimethyl-4-aza-5α-pregn-1-en-3-one,

- 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
5 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
15 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
20 17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one.  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
25 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
30 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,



- 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one, and  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one.  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
5 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
15 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
4,7 $\beta$ ,20-trimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
25 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
30 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,

- 17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
5 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
10 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
15 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
20 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
25 17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one, and  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one.
- 30                    3.     The method of Claim 1 wherein the compound of  
structural formula I is 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one.
4.     The method of Claim 1 wherein the subject is a  
human.

5. The method of Claim 1 wherein the compound of structural formula I is administered at a dose of 0.01 to 1000 mg per day.

5 6. The method of Claim 5 wherein the compound of structural formula I is administered at a dose of 0.1 to 50 mg per day.

7. The method of inhibiting bone loss in a subject in need of such treatment according to Claim 1 comprising administration of an effective amount of the compound of structural formula I and an effective amount of a bone anabolic agent or a bone antiresorptive agent or an inhibitor of 5 $\alpha$ -reductase type 2 or a dual 5 $\alpha$ -reductase inhibitor.

8. The method according to Claim 7 wherein the bone anabolic agent is selected from a form of parathyroid hormone and a growth hormone secretagogue, growth hormone, growth hormone releasing hormone and insulin-like growth factor.

9. The method according to Claim 8 wherein the growth hormone secretagogue is selected from:

- (a) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and
- (b) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

10. The method according to Claim 7 wherein the bone antiresorptive agent is selected from:

- (1) an estrogen,
- (2) a bisphosphonate compound, and
- (3) an antiestrogenic compound.

11. The method according to Claim 10 wherein:  
(1) the estrogen is selected from:

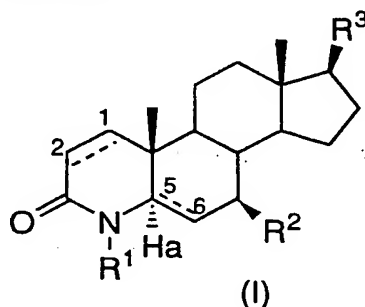
- (a) 17 $\beta$ -estradiol,  
(b) estrone,  
(c) conjugated estrogen, equine estrogen, and  
(d) 17 $\beta$ -ethynyl estradiol;
- 5 (2) the bisphosphonate compound is selected from:  
(a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,  
(b) N-methyl-4-amino-hydroxybutylidene-1,1-  
bisphosphonic acid,  
(c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-  
10 bisphosphonic acid,  
(d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic  
acid,  
(e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-  
bisphosphonic acid,  
(f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-  
15 1,1-bisphosphonic acid,  
(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic  
acid, and  
(h) 4-(hydroxymethylene-1,1-bisphosphonic  
20 acid)piperidine; and
- (3) the antiestrogenic compound is selected from:  
(a) raloxifene,  
(b) clomiphene,  
(c) zuclomiphene,  
25 (d) enclomiphene,  
(e) nafoxidene,  
(f) CI-680,  
(g) CI-628,  
(h) CN-55,945-27,  
30 (i) Mer-25,  
(j) U-11,  
(k) 555A, and  
(l) U-100A;

and pharmaceutically acceptable salts thereof.

12. The method of inhibiting bone loss in a subject in need of such treatment according to Claim 11 comprising administration of 0.1 to 50 mg/day of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one together with 2.5 to 100 mg/day of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

13. The method according to Claim 7 wherein:  
the 5 $\alpha$ -reductase type 2 inhibitor is selected from:  
10 (a) finasteride, and  
(b) epristeride; and  
the dual 5 $\alpha$ -reductase inhibitor is:  
(a) 17 $\beta$ -N-(2,5-bis(trifluoromethyl))phenyl carbamoyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

14. A method of treating and preventing a disease involving bone resorption selected from: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease which comprises the administration to a subject in need thereof of an effective amount of a compound of structural formula I:



wherein:

the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;  
R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and  
R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally  
having one degree of unsaturation;  
or a pharmaceutically acceptable salt thereof.

5

15. The method of Claim 14 wherein the compound of structural formula I is selected from:

- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,
- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,
- 10 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,
- 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,
- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,
- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,
- 15 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,
- 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 4,7 $\beta$ ,20-trimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 20 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,
- 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,
- 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 25 17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 30 17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,
- 17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,

- 17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
5 17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one.  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,  
10 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
15 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one, and  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one.  
20 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
25 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
30 17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-17-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one ,

- 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregnan-3-one,  
5 20-ethyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
4,7 $\beta$ ,20-trimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregnan-3-one,  
10 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
15 17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
20 17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -(5-methylhexyl)-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-propyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
25 17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androstan-3-one,  
17 $\beta$ -n-butyl-4,7 $\beta$ -dimethyl-4-aza-5 $\alpha$ -androstan-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1,17-dien-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
30 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,



- 17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
20-ethyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
5 20-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -pregn-1-en-3-one,  
17 $\beta$ -n-propyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -n-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -isobutyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17 $\beta$ -tert.-butyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17 $\beta$ -n-pentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one, and  
17 $\beta$ -isopentyl-7 $\beta$ -methyl-4-aza-5 $\alpha$ -androst-1-en-3-one;

or a pharmaceutically acceptable salt thereof.

- 15                    16.    The method of Claim 14 wherein the compound of  
structural formula I is 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one.
17.    The method of Claim 14 wherein the compound of  
structural formula I is administered at a dose of 0.01 to 1000 mg per day.
- 20                    18.    The method of Claim 14 wherein the compound of  
structural formula I is administered at a dose of 0.1 to 50 mg per day.
19.    The method of treating and preventing a disease  
25 involving bone resorption selected from: osteoporosis, osteopenia,  
Paget's disease, malignant hypercalcemia, periodontal disease, joint  
loosening and metastatic bone disease in a subject in need thereof  
according to Claim 14 comprising administration of an effective amount  
of the compound of structural formula I and an effective amount of a  
30 bone anabolic agent or a bone antiresorptive agent or a 5 $\alpha$ -reductase type  
2 inhibitor or a dual 5 $\alpha$ -reductase inhibitor.
20.    The method according to Claim 19 wherein the bone  
anabolic agent is selected from a form of parathyroid hormone and a

growth hormone secretagogue, growth hormone, growth hormone releasing hormone and insulin-like growth factor.

21. The method according to Claim 20 wherein the growth hormone secretagogue is selected from:

- (a) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and
- (b) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

22. The method according to Claim 19 wherein the bone antiresorptive agent is selected from:

- (1) an estrogen,
- (2) a bisphosphonate compound, and
- (3) an antiestrogenic compound.

23. The method according to Claim 22 wherein:

- (1) the estrogen is selected from:
  - (a) 17 $\beta$ -estradiol,
  - (b) estrone,
  - (c) conjugated estrogen, equine estrogen, and
  - (d) 17 $\beta$ -ethynyl estradiol;
- (2) the bisphosphonate compound is selected from:
  - (a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,
  - (b) N-methyl-4-amino-hydroxybutylidene-1,1-bisphosphonic acid,
  - (c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-bisphosphonic acid,
  - (d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,
  - (e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid,

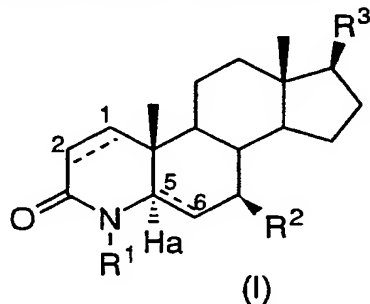
- (f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid,  
(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid, and  
5 (h) 4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine; and  
(3) the antiestrogenic compound is selected from:  
(a) raloxifene,  
(b) clomiphene,  
10 (c) zuclomiphene,  
(d) enclomiphene,  
(e) nafoxidene,  
(f) CI-680,  
(g) CI-628,  
15 (h) CN-55,945-27,  
(i) Mer-25,  
(j) U-11,  
(k) 555A, and  
(l) U-100A;  
20 and pharmaceutically acceptable salts thereof.

24. The method according to Claim 23 comprising administration of 0.1 to 50 mg/day of 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one together with 2.5 to 100 mg/day of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.  
25

25. The method according to Claim 19 wherein:  
the 5 $\alpha$ -reductase type 2 inhibitor is selected from:  
(a) finasteride, and  
30 (b) epristeride; and  
the dual 5 $\alpha$ -reductase inhibitor is:  
(a) 17 $\beta$ -N-(2,5-bis(trifluoromethyl))phenyl carbamoyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

26. The method according to Claim 14 wherein the bone resorption disease being prevented or treated is osteoporosis.

27. A pharmaceutical composition comprising a  
 5 pharmaceutically acceptable carrier, and a therapeutically effective amount of a compound of structural formula I:



wherein:

10 the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;

R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

15 R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and

R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;

or a pharmaceutically acceptable salt thereof.

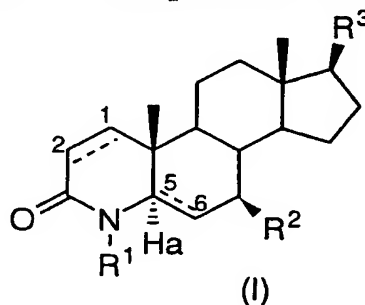
20 28. A pharmaceutical composition according to Claim 27 comprising a pharmaceutically acceptable carrier, a therapeutically effective amount of the compound of structural formula I and a therapeutically effective amount of another agent selected from:

- 25
- (1) a form of parathyroid hormone,
  - (2) a growth hormone secretagogue,
  - (3) growth hormone,
  - (4) growth hormone releasing hormone,
  - (5) insulin-like growth factor,
  - (3) an estrogen,

- (4) a bisphosphonate compound, and
- (5) an antiestrogenic compound.

29. The pharmaceutical composition according to Claim  
 5 28 comprising 0.1 to 50 mg 7 $\beta$ ,20-dimethyl-4-aza-5 $\alpha$ -pregn-1-en-3-one and  
 2.5 to 100 mg 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

30. The use of a compound of structural formula I:



10 wherein:

the C1-C2 and C5-C6 bonds designated with a dotted line each  
 independently represent a single or double bond, provided  
 that when the C5-C6 is a double bond, H<sub>a</sub> is absent and  
 when the C5-C6 bond is a single bond H<sub>a</sub> is present and  
 15 represents hydrogen;

R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

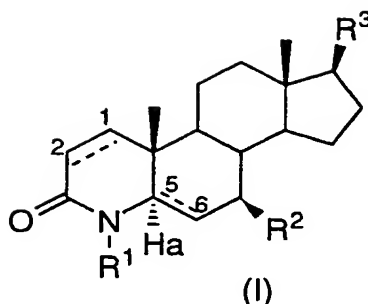
R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and

R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally  
 having one degree of unsaturation;

20 or a pharmaceutically acceptable salt thereof;

for the preparation of a medicament useful to inhibit bone loss:

31. The use of a compound of structural formula I:



wherein:

the C1-C2 and C5-C6 bonds designated with a dotted line each independently represent a single or double bond, provided that when the C5-C6 is a double bond, H<sub>a</sub> is absent and when the C5-C6 bond is a single bond H<sub>a</sub> is present and represents hydrogen;

R<sup>1</sup> is selected from hydrogen and C<sub>1-5</sub> alkyl;

R<sup>2</sup> is C<sub>1-5</sub>alkyl, either straight or branched chain; and

R<sup>3</sup> is C<sub>3-7</sub>alkyl, either straight or branched chain, optionally having one degree of unsaturation;

or a pharmaceutically acceptable salt thereof;

for the preparation of a medicament useful to prevent or treat a disease involving bone resorption selected from: osteoporosis, osteopenia,

Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease.

32. The use according to Claim 31 of 7β,20-dimethyl-4-aza-5α-pregn-1-en-3-one for the preparation of a medicament useful to prevent or treat a disease involving bone resorption selected from: osteoporosis and osteopenia.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/22050

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/56

US CL : 514/177

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/177

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,527,807 A (BAKSHI et al.) 18 June 1996, column 5, lines 55-60, compound V, column 7, lines 1-15, compound XI.	27-29
X	US 5,237,064 A (BAKSHI et al.) 17 August 1993, claim 1, parts (a) and (c).	27-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* B* earlier document published on or after the international filing date	* Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A* document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means	
* P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 MARCH 1998

Date of mailing of the international search report

13 APR 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
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Form PCT/ISA/210 (second sheet)(July 1992)\*

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/22050

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAPLUS, BIOSIS, MEDLINE, EMBASE, REGISTRY structure search with the following terms: bone or osteop? or paget? pr hypercalcem? or periodont? or joint? or metastat?, antiresorp? or anaboic or reductase, parathyroid hormone or growth hormone or insulin, dimethyl(l)aza(l0(pregn or pregnan)(l)(one)